
A model for neural development and treatment of rett syndrome using human induced pluripotent stem cells.

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Public Summary:

Autism spectrum disorders (ASD) are complex neurodevelopmental diseases. Using Rett syndrome (RTT) as an ASD prototype, we generated induced pluripotent stem cells (iPSCs). Neurons derived from RTT-iPSCs had fewer synapses and altered connectivity when compared to control neurons. In addition, we used drugs to rescue synaptic defects in RTT neurons, indicating that autistic neurons can be reverted. Our data provide evidence of a developmental window in an autistic syndrome, where potential therapies could be successfully employed. Moreover our model recapitulates early stages of a human neurodevelopmental disease and represents a promising cellular tool for drug screening, diagnosis and personalized treatment.

Scientific Abstract:

Autism spectrum disorders (ASD) are complex neurodevelopmental diseases in which different combinations of genetic mutations may contribute to the phenotype. Using Rett syndrome (RTT) as an ASD genetic model, we developed a culture system using induced pluripotent stem cells (iPSCs) from RTT patients' fibroblasts. RTT patients' iPSCs are able to undergo X-inactivation and generate functional neurons. Neurons derived from RTT-iPSCs had fewer synapses, reduced spine density, smaller soma size, altered calcium signaling and electrophysiological defects when compared to controls. Our data uncovered early alterations in developing human RTT neurons. Finally, we used RTT neurons to test the effects of drugs in rescuing synaptic defects. Our data provide evidence of an unexplored developmental window, before disease onset, in RTT syndrome where potential therapies could be successfully employed. Our model recapitulates early stages of a human neurodevelopmental disease and represents a promising cellular tool for drug screening, diagnosis and personalized treatment.

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